

Diallate
Position Document 1

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Diallate: Position Document 1

Prepared by
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U.S. Environmental Protection Agency
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I. BACKGROUND

A. Nomenclature

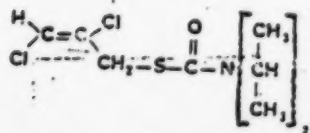
Diallate is marketed under the trade name, AVAD^R. Other names that have been used are CP 15 336 and DATC. The American Chemical Society's Chemical Abstracts Service has assigned the name S-(2,3-dichloro-2-propenyl)bis(1-methylethyl)carbamothioate and the number CAS 230 3-16-4 to diallate. S-(2,3-Dichlorallyl)diisopropylthiocarbamate is the name placed on labels of pesticide products.

B. Chemistry

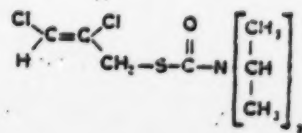
1. General

Diallate is a volatile, amber colored liquid with a melting point of 25-30°C. It is soluble in most organic solvents but only slightly soluble in water (14 ppm at 25°C).

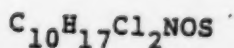
Structural Formula:



trans isomer



cis isomer



Molecular weight: 270.2

2. Residues in Food

The only available information on diallate residues in food comes from data submitted by Monsanto in their tolerance requests of 1967 (Pesticide Petition #607) and 1969 (Pesticide Petition #832). In PP#607, data on 49 samples of 13 crops (an average of 4 samples/crop) indicated that diallate residues were below 0.1 ppm. However, the analytical methodology used to obtain this data was less sensitive (0.1-0.2 ppm) when compared with the methodology (<0.02 ppm) followed in the study submitted in PP#832. The latter data was obtained from 17 samples from 5 additional crops and 2 crops previously studied for PP#607. Residues were not found at or above the level of the method of detection, < 0.02 ppm.

Analysis for diallate residues has never been done by the Food and Drug Administration Total Diet Program (Market Basket Survey) or by the U.S. Department of Agriculture meat and poultry inspection program. Joint meetings of the World Health Organization and the Food and Agriculture Organization on pesticide residues have never reviewed residue data on diallate.

3. Fate in the Environment

a. Water

No information is currently available on the fate of diallate in water.

b. Air

Diallate has a vapor pressure of 1.5×10^{-4} mm Hg at 25°C. Its evaporation rate is 10.63×10^{-9} mol/cm hr at 20°C (1). Since diallate is volatile, use directions recommend incorporation into the upper 2 inches of soil as soon as possible after application, preferably on the day of application.

Diallate is not currently included in the EPA National Air Monitoring Program for Pesticides.

c. Soil

Diallate has been reported to disappear most rapidly from soils containing living microbial populations (2). In experiments with radiolabeled diallate, 50% of the diallate applied initially (2.5 ppm) had disappeared after 1.5 to 4 weeks in nonsterile soils compared with 20 weeks for sterile soils. This disappearance has been reported to be a result of degradation by soil microflora rather than by volatilization, adsorption or retention by soil microflora. Other studies have reported the degradation of diallate by isolated soil fungi (3). Mills and Alley report two major information gaps on diallate: (a) the effect of diallate on the major soil biota and (b) the identity of plant and soil metabolites of diallate (4).

Analysis for diallate residues is not currently included in the EPA National Soils Monitoring Program.

d. Plants

Plant metabolism studies with radiolabeled diallate on seedlings of barley, flax and sugar beets were submitted in PP#607. These studies showed that diallate was rapidly metabolized by the plants. The slowest rate was observed for barley where 74% of the radioactivity was released as labelled CO₂ after 11 days. The fastest release was in sugar beets with 87% of the radioactivity released as CO₂ after 6 days.

C. Manufacturing Process, Technical Products and Formulations

Diallate is prepared by reacting a mixture of diisopropylamine and 1,2,3-trichloropropene with carbonyl sulfide (5).

Technical diallate is available to formulators at 90% purity. The remaining 10% consists of unreacted intermediates from the manufacturing process which are unknown to EPA. The identity of this material has been requested from the supplier and will be evaluated for potential hazard (6).

Diallate formulations include a granular product that contains 10% active ingredient and an emulsifiable concentrate that contains 4 lb active ingredient/gal. The granular product may be used on sugar beets only. The

granular product may be used on sugar beets only. The most common form is the emulsifiable concentrate which is sprayed directly onto the soil surface. Commercial formulations contain roughly equal amounts of the cis and trans isomers (7).

D. Production

Monsanto Chemical Company is the sole producer of technical diallate in the United States. Production data is confidential information under Sections 7(c) and 10 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and is therefore presented in Table 1 for EPA use only. The International Agency for Research in Cancer estimates that annual production of diallate in Europe is in the range of 1 to 5 million kg (5).

E. Registered Uses

Diallate has been used in the United States as a selective preemergence herbicide since 1960. Current registered uses are for the control of wild oats in sugar beets, flax, barley, corn, forage legumes (alfalfa, alsike clover, red clover, sweet clover), lentils, peas, potatoes, and soybeans. Registered uses also include control of other grasses and broadleaf weeds in sugar beets when combined with pebulate or cycloate. Diallate is applied directly to

the soil by spray, broadcast or band methods in the fall just before the freeze or in the spring before or after seeding but not after emergence. Incorporation into the soil after application is required. Usually only one application per season is made. There are eight Federal registrations of products containing diallate which are held by three registrants.

II. REGULATORY HISTORY

An experimental use permit was obtained by Monsanto in May 1960 for the use of diallate on barley, flax, sugar beets, rapeseed, and sunflowers.

The first registration for a product containing diallate was granted December 9, 1960, to Monsanto (EPA Registration Number 524-119). Use of diallate on corn, forage legumes, lentils, peas, potatoes, safflower and sugar beets was approved because no residues were detected on these foods.

Monsanto had originally requested (Pesticide Petition #607) a tolerance of 0.3 ppm for diallate on the above crops plus soybeans. These tolerances were not granted because of inadequacies in residue and toxicity data submitted by the petitioner. Toxicity data submitted for a 90-day dog feeding study were considered inadequate to

establish a "no effect" level (NEL). Ovarian and testicular changes were noted during microscopic examination of these tissues. This petition was withdrawn in December 1967.

A second petition (PP#832) was filed by Monsanto in June 1969 for negligible residue tolerances of 0.05 ppm for diallate on corn, forage legumes, lentils, peas, potatoes, safflower, sugar beets, and soybeans. These additional residue data, obtained by a more sensitive analytical method, satisfied the reviewers that they would not expect residues to transfer to meat, milk, eggs and poultry since no crop residues greater than the background of the untreated samples (<0.02 ppm) were found. Monsanto resubmitted the toxicity data that was in PP#607, including the 90-day dog study, but this time a NEL of 3.3 mg/kg/day (25 ppm) was determined for testicular and ovarian changes in the dog. The toxicology review concluded that the proposed tolerances provided an adequate margin of safety to man based on the dog NEL.

Establishment of the 0.05 ppm tolerances was delayed, however, pending the report of the Department of Health, Education and Welfare Secretary's Commission on Pesticides and Their Relationship to Environmental Health, chaired by Dr. Emil M. Mrak. When this report was issued in December 1969, it recommended that human exposure to diallate be minimized because of evidence of tumor induction in mice fed diallate at 560 ppm for 18 months (8). The Commission judged that these tests were adequately conducted.

After consideration of the Mrak report and the cited mouse studies, the Toxicology Branch, Food and Drug Administration, concluded that with the 2000-fold safety factor, an adequate margin of safety for man was provided by the 0.05 ppm tolerances (9). Tolerances were established on July 28, 1971 (40 CFR 180.277).

III. SUMMARY OF SCIENTIFIC EVIDENCE TO SUPPORT REBUTTABLE PRESUMPTION

The Working Group has determined that the following adverse effects of diallate meet or exceed the criteria for issuance of a rebuttable presumption against registration (RPAR).

A. Oncogenic Effects in Test Animals

As provided in 40 CFR Section 162.11(a)(3)(ii)(A), the induction "of oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure" is basis for an RPAR.

1. Mice

The only study of oral administration of diallate to mice was conducted by Innes et al. and resulted in an increased incidence of liver-cell and pulmonary tumors (10,11). This study provided the basis for the Mrak Commission recommendation that human exposure to diallate be minimized (see section on Regulatory History).

In a 1976 evaluation of the carcinogenic risk of diallate, a working group of the United Nations International Agency for Research on Cancer (IARC) concluded that diallate is carcinogenic in mice after oral administration on the basis of the Innes study (5).

The EPA Carcinogen Assessment Group (CAG) subsequently reviewed this study and concluded that "In mice, the Innes study showed statistically significant and pronounced increases in hepatoma incidence in males of the two tested strains. There were small but statistically significant increases in the incidence of lung adenomas in both sexes in one strain (X) of mice and in males only of the other strain (Y)" (12).

2. Rats

In addition to the above mouse study, there have been two studies of long-term oral administration of diallate to rats.

An abstract appeared in 1973 on a study conducted by Ulland et al. at Litton-Bionetics (13). No further information was available for the 1976 IARC working group so their monograph concluded that "inadequate reporting does not allow an evaluation of this experiment" (5). Since the IARC evaluation, the EPA Office of Special Pesti-

cide Reviews (OSPR) has received data verified by the National Cancer Institute on this study (14). Details of this study are given in the CAG report (12). In their review of this study, CAG concluded "the Litton Bionetics study showed a statistically significant increase in malignant tumors, as a whole, only at the highest dose in male rats and only at the lower dose in female rats."

Industrial Bio-Test also conducted a rat study in which they concluded "that the neoplastic lesions noted in the test and controls were considered normal for rats of this age and strain" (15).

After evaluating this study, CAG concluded, "the Industrial Bio-Test study in rats showed a statistically significant excess of mammary carcinomas in females" (12).

On the basis of these two studies, the Diallate Working Group concluded that the evidence of oncogenicity from long-term oral administration of diallate to mice and rats supports the issuance of an RPAR.

IV. Other Adverse Effects

This section addresses certain adverse effects which diallate may produce but for which insufficient evidence exists to issue a rebuttable presumption. The Working Group recommends that the Agency solicit comment on the evidence presented below and encourage the submission of additional studies or relevant information on these effects.

A. Neurotoxicity

As provided in 40 CFR Section 162.11(a)(3)(ii)(B), the production of "any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety" is a basis for a RPAR.

Neurotoxic effects were observed in a recent study in which chickens were administered diallate (16). Ten hens over 9 months old were administered 0.312 g/kg body weight diallate by gavage twice daily for 3 consecutive days. This dosing procedure was repeated for 3 more consecutive days beginning on test day 21. The total cumulative dosage for the 6 days was 3.74 g/kg. The study also included negative and positive control groups of 10 hens. The positive control group received triortho cresyl phosphate (TOCP) at an unreported dosage level and regimen. At the end of the 42-day test period, all surviving hens from the negative control and test groups were sacrificed and subjected to a gross pathological examination. All positive control hens were sacrificed in extremis on day 16. Hematoxylin-eosin-stained sections of brain, spinal cord and sciatic nerve from all negative control, diallate-treated and 4 of 10 positive control hens were examined microscopically.

Test hens showed moderate to severe clinical signs of neurotoxicity within 48 hours after the beginning of both dosing periods. Ataxia, weakness of wings and legs and inability to stand continued through the 42-day test period but decreased to some extent.

Three of the 10 test hens died during the test (on days 27, 28 and 39) after exhibiting paralysis. A fourth hen was sacrificed in extremis on day 31 after exhibiting paralysis for 6 days. Histologic evaluation of the sacrificed hen revealed mild demyelination of the peripheral sciatic nerve, moderate multifocal axonal degeneration of the spinal cord and mild axonal degeneration of the brain. The only other test hen showing treatment-induced lesions was the one that died on day 27. Minimal to mild axonal degeneration was present in the sciatic nerve of this hen.

Evaluations of this study by EPA (17) and by an EPA contractor (18) concluded that the study provides adequate evidence that diallate produces a neurotoxic effect at the dosage level used but that it does not provide adequate evidence to determine a dose-response relationship.

In the absence of evidence demonstrating a no effect level after repeated administration, it is not possible to determine an adequate margin of safety for the

human population (19). The registrant has notified the Agency that he is conducting a study to determine a dose response relationship (20). Should evaluation of this or any other study that comes to our attention provide an adequate basis for an RPAR a supplemental Position Document and Federal Register notice will be issued. In addition the Agency has the option to initiate cancellation proceedings on this basis without prior resort to the RPAR process, pursuant to 40 CFR 162.11(a)(6).

B. Mutagenicity

Regulations in 40 CFR 162.11(a)(3)(ii)(A) require that an RPAR be issued if "mutagenic effects, as determined by multitest evidence" are induced by the pesticide.

Two different types of mutagenic studies have been reported for diallate: a dominant lethal study in mice (21) and a bacterial study (Ames Test) (22).

These studies were evaluated by an EPA contractor who concluded that while mutagenic effects were not induced in either of these studies, additional studies are required to evaluate mutagenic risk (23).

In the guidelines for dominant lethal tests published by the Canadian government, negative results are not considered meaningful "unless derived from tests carried out at

different dosage levels with different dosage regimes" (24). Although the available dominant lethal study for diallate concludes that diallate produced no mutagenic effect, it is limited because the investigator used only two dose levels instead of the three-four dose levels recommended as good protocol.

The negative result of the published bacterial study can only be considered tentative since no metabolic activation system was included.

Very recently, a third mutagenicity study (Ames Test) was received in prepublication form (25), but an evaluation could not be done in time for inclusion in this document. It is recognized the many carbamate pesticides produce an arrest in cell division at metaphase (c-mitosis) in-plants (26). We solicit information concerning the activity of diallate on plant and animal cell division. Should evaluation of this or any other study that comes to our attention provide adequate basis for an RPAR, a supplemental Position Document and Federal Register notice will be issued. In addition, the Agency has the option to initiate cancellation proceedings on this basis without prior resort to the RPAR process, pursuant to 40 CFR 162.11(a)(6).

C. Reproductive Effects

Effects on reproduction are of concern in view of the effects observed in the 90-day dog study submitted in

support of tolerance requests (see section on Regulatory History). This study is currently being reevaluated.

A teratogenic study in albino rabbits was also submitted (27). In evaluating this study, an EPA contractor concluded that diallate was not teratogenic or fetotoxic in rabbits (23).

A three-generation reproduction study in rats is currently in progress. An interim report was submitted by Monsanto with data on the Fo generation only (28). It is not possible to make conclusions from these data.

Evaluation of these studies will be pursued and if these or any other studies provide adequate basis for an RPAR on reproductive effects, a supplemental Position Document and Federal Register notice will be issued. In addition, the Agency has the option to initiate cancellation proceedings on this basis without prior resort to the RPAR process, pursuant to 40 CFR 162.11(a)(6).

V. Recommendation

The Working Group recommends that the Agency solicit comment on the fate and effects of diallate and its impurities on the environment specifically (a) the identity of metabolites and degradation products and their rates of formation in all media, especially water; and (b) their effect upon flora and fauna especially those with a metabolism similar to man.

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